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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/524,945	02/16/2005	Farhad Parhami	58086-241892	3129

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EXAMINER	
LEAVITT, MARIA GOMEZ	
ART UNIT	PAPER NUMBER
1633	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/524,945	PARHAMI, FARHAD	
	Examiner	Art Unit	
	MARIA LEAVITT	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *4,5,9,10,18,22,27 and 29-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6-8,11-17,19-21,23-26 and 28* is/are rejected.

7)☒ Claim(s) *1,2,13 and 14* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 February 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10-10-2007;01-11-2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Claim status. Claims 1-41 are pending. Applicant's election **without traverse** of Group I, drawn to claims 1-28, in the reply filed on 03/31/2008 is acknowledged. In the same reply, Applicant elected **without traverse** the following species: 20-S hydroxycholesterol as the oxysterol, the combination of 20S-hydroxycholesterol and 22S-hydroxycholesterol, bisphosphonates as the secondary agent, osteoprogenitor cells as the mammalian cell and expression of osteocalcin mRNA as the biological marker. Upon further consideration, the examiner has decided to withdraw the restriction requirements among the following species: 20-S hydroxycholesterol as the oxysterol, the combination of 20S-hydroxycholesterol and 22S-hydroxycholesterol, osteoprogenitor cells as the mammalian cell and expression of osteocalcin mRNA as the biological marker because prior art consideration and/or examination of arts relevant to the claimed species as a whole would not be unduly burdensome. Claims 4, 5, 9, 10, 18, 22, and 27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, and claims 29-41 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Therefore, claims 1-3, 6-8, 11-17, 19-21, 23-26 and 28 are currently under examination to which the following grounds of rejection are applicable.

Specification

The disclosure is objected to because of the following informalities: this application contains sequence disclosures (p. 15, paragraph [0069]) that are encompassed by the definitions for

nucleotide sequences set forth in 37 CFR 1.821 (a)(1) and (d). However, the specification fails to comply with the requirements of 37 CFR 1.821 (a)(1) and (d), because the sequence identifiers, preceded by SEQ ID NO are missing.

Appropriate correction is required.

Claim Rejections - 35 USC § 103

The instant claims are examined to the extent that they read on the elected species bisphosphonates as the secondary agent.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 6-8, 11-17, 19-21, 23-26 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Paralkar et al., US Publication no. 20040176423 (Date of Publication September 9, 2004), in view of Parish et al., (1995, Lipids, pp. 247-251) and further in view of Wang et al. (Clinical Orthopaedics and Related Research, 2000, 370: 295-310)

Paralkar et al. teaches *in vitro* and *in vivo* methods for enhancing bone formation in mammals, including humans, comprising administration of compositions comprising 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors such as statins and prostaglandin agonists (p. 1, paragraph [0010]). In relation to cell culture of progenitor osteoblastic cells,

Paralkar et al. discloses that statins stimulate bone formation *in vitro* and enhances osteoblast cell numbers at all stages of differentiation (p. 1, paragraph [0011]; p.3 paragraph [0051]). Indeed, Paralkar et al. describes an enhanced expression of the mRNA for bone morphogenic protein-2 (BMP-2) (e.g., BMP2 expression induces osteoblast differentiation) in cultured murine 2T3 cells or human MG-63 bone cells (i.e., osteo-progenitor human osteoblast) resulting from exposure of said cells to statins (p.3, paragraphs [0051] [0053]). Moreover, Paralkar et al. teaches *in vivo* treatment with statins and promotion of healing of bone fractures (p. 6, paragraphs [0083]-[0084]). (**Current claims 1).** Paralkar et al. also teach a method of stimulating mammalian cells to express biological differentiation markers (p.3, paragraph [0053]). **(Current claim 6, in part)** Paralkar et al. describes effective therapeutic does of statins that are titrate to achieve bone mass augmentation)(p. 5,paragraphs [0077]-[0078]). Furthermore, Paralkar et al. discloses that bisphosphonates are anti-resorptive agents used to combat osteoporosis and contemplates their administration with a HMG-CoA reductase inhibitor as a therapy for bone conditions (p. 1, paragraphs [0007] and [0018]) (**Current claims 23 and 28**).

Paralkar et al. does not specifically teach osteblastic differentiation with one oxysterol.

However, at the time the invention was made, Parish et al., discloses that side-chain oxysterols are known to be potent inhibitors of HMG-CoA reductase, including derivatives of cholesterol including 25- or 26- positions and side-chain hydroxylation at 20 α- and 22R-positions (All document, particularly Abstract, p. 248, col. 2; p. 250, col. 1, paragraph 2) . (**Current claims 2, 7, 13, 14, 15, 16, 19, 20, 24 and 25**). In addition, Paralkar et al., discloses at page 250, Tables 1-3, the relative potency of a wide number of oxysterols that inhibit HMG-CoA

reductase, which exhibit synergism in the reduction of the levels of HMG-CoA reductase activity (p. 250, col. 2, paragraph 2) (Current claims **3, 8, 17, 21 and 26**)

The combined references fail to teach mammalian mesenchymal cells and inhibition of adipogenesis.

However, at the time the invention was made, Wang et al. teaches that treatment with statins (e.g., lovastatin) inhibits adipocyte differentiation and induces osteoblastic differentiation of mouse MSCs (e.g., pluripotent mesenchymal cells, D1) as indicated by markers such as alkaline phosphatase activity, osteocalcin mRNA and cAMP production (**claims 11 and 12**) (Abstract, p. 297, col. 1 last paragraph; col. 2, paragraph 1; p. 299, col. 1; p. 300, col. 1; p. 307, col. 2, paragraph 1).

Therefore, in view of the benefits of enhancing bone formation in mammalian cells by using inhibitors of HMG-CoA reductase such as statins, it would have been *prima facie* obvious for one of ordinary skill in the art, on teachings provided by the combined cited references, to modify the composition of Paralkar et al. to replace statins with any side-chain oxysterols, particularly because Parish et al., discloses that it is well known in the art that oxysterols repress HMG-CoA reductase. The substitution of statins by side-chain oxysterols would achieve the predictable results of inducing osteoblastic differentiation as both compounds repress the same HMG-CoA reductase. Likewise, it would have been *prima facie* obvious for one of ordinary skill in the art, in an attempt to optimize the reduced levels of HMG-CoA reductase activity, to combine any of the disclosed side-chain oxysterols inhibiting HMG-CoA reductase as Parish et al., teaches their synergism reducing this enzyme. Moreover, it would have been *prima facie* obvious as a matter of design of choice, to use MSC to achieve the predictable result of

obtaining osteoblasts and inhibiting adipocyte differentiation, particularly because Wang et al. successfully demonstrates decreased lipid accumulation and prevention of bone death in differentiated MSC after treatment with statins. One of ordinary skill in the art would have had a reasonable expectation of success in generating a method to induce osteblastic differentiation of MSC by treating said cells with at least one oxysterol as evidenced by the production of said method in the instant specification by following the combined teachings of Paralkar, Parish and Wang.

Provisional Rejection, Obviousness Type Double Patenting-

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3, 6-8, 11-17, 19-21, 23-26 and 28 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 5-9, 11-15, 17-20, 22-25 and 27-30 of copending Application No. 10,569,994, in view of Paralkar et al.,

20040176423 (Date of Publication September 9, 2004). Although the conflicting claims are not identical, they are not patentably distinct from each other because they are obvious variants.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The claims of copending Application No. 10,569,994, are drawn to (i) a method of inducing osteoblastic differentiation of mesenchymal stem cells (claims 1-5), (ii) a method of stimulating mammalian cells to express an osteoblastic differentiation marker, wherein the marker is osteopontin and wherein the mammalian cells are mesenchymal stem cells, osteoprogenitor cells, or calvarial organ cultures (claims 6-12), and (iii) a method of inhibiting adipocyte differentiation of mesenchymal stem cells (claims 13-17), (iv) methods of treating a patient to induce bone formation (claims 18-27), and (v) methods of treating a patient exhibiting symptoms of osteoporosis (claims 28-32). All methods require treating the cells with a combination of at least one oxysterol and bone morphogenic protein (BMP); the methods further comprise using secondary agents, such as bisphosphonates.

The instant claims are drawn to (i) a method of inducing osteoblastic differentiation of mesenchymal stem cells (claims 1-5), (ii) a method of stimulating mammalian cells to express an osteoblastic differentiation marker, wherein the marker is osteopontin and wherein the mammalian cells are mesenchymal stem cells, osteoprogenitor cells, or calvarial organ cultures (claims 6-12), (iii) a method of inhibiting adipocyte differentiation of mesenchymal stem cells with at least one oxysterol (claims 13-14), (iv) methods of treating a patient to induce bone formation (claims 15-23), and (v) methods of treating a patient exhibiting symptoms of

osteoporosis (claims 24-28). All methods require treating the cells with at least one oxysterol; the methods further comprise using secondary agents, such as bisphosphonates.

The instant claims differ from claims 1-3, 5-9, 11-15, 17-20, 22-25 and 27-30 by no requiring in the combination a bone morphogenic protein (BMP).

However, at the time the invention was made, Paralkar et al., exemplified prior art that teaches that bone morphogenic proteins (BMPs) are known to enhance osteoblast differentiation (p.3, paragraph [0051]).

Therefore, in view of the benefits of enhancing bone formation in mammalian mesenchymal cells by using at least one oxysterol, it would have been *prima facie* obvious for one of ordinary skill in the art, to modify the instantly claimed composition to include any of the BMPs as taught by Paralkar et al., in an attempt to enhance bone formation in mammalian mesenchymal stem cells.

Claims 1-3, 6-8, 11-17, 19-21, 23-26 and 28 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 of copending Application No. 11/918,089 and over claims 1-9 and 15 of the copending Application No. 11/991,322. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are obvious variants.

The instant claims and the claims of the Application No. 11/918,089 and 11/991,322 are obvious variants because all three applications are broadly drawn to methods of inducing osteoblastic differentiation and reducing adipogenesis in mammalian mesenchymal stem cells by treating cells with at least one oxysterol and optionally with a secondary agent.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim objection

Applicant is advised that should claims 1 and 2 be found allowable, claim 13 and 14 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

It is noted that, although the preamble is different, the method of claims 1 and 2 and the method of claims 13 and 14 are identical because they both recite the same steps and compositions, i.e., treating mesenchymal stem cells with at least one oxysterol. Therefore, the claimed method of inducing osteoblastic differentiation of mesenchymal stem cells would necessarily and inherently be a method of inhibiting mesenchymal stem cell proliferation to adipocytes given the guidance of the present specification; conversely, the claimed method of inhibiting differentiation of mesenchymal stem cells would necessarily be a method of inducing their differentiation to osteoblasts.

Conclusion

Claims 1-3, 6-8, 11-17, 19-21, 23-26 and 28 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/Maria Leavitt/

Maria Leavitt, PhD
Examiner, Art Unit 1633